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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,936	10/23/2003	Jane Hirsh	CP 107M (2)	1596

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EXAMINER	
SHEIKH, HUMERA N	
ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/691,936	HIRSH ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/1/07; 5/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of Applicant's Arguments/Remarks filed 07/05/07 and the Information Disclosure Statements (IDS) filed 03/01/07 & 05/23/07 is acknowledged.

The Restriction Requirement filed 06/29/07 has been withdrawn, by virtue of Applicant's persuasive remarks.

The previous Non-Final Office Action filed 01/12/07 has also been withdrawn. The following are the new grounds of rejection:

Claims 1-22 are pending in this action. Claims 1 and 3 have been amended. Claims 1-22 are rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, 19 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the limitation "diminished incidence or reduced intensity" is vague in the sense that it does not provide any upper or lower levels of incidence or intensity reduction. To what certain extent or levels is the incidence/intensity diminished or reduced? Clarification is requested.

Claim 4, line 3 recites "followed by a slow or extended release". The limitation "slow or extended drug release" renders the claim indefinite because it is unclear as to what extent of duration is encompassed by "slow release" or "extended release". How much of a slow or extended release is Applicant referring to?

Claim 5 recites the limitation "wherein the defined period of time" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 19, line 3 recites the limitation "over a period of time". The limitation is indefinite because it is unclear as to what duration of time Applicant referring to? The limitation is vague and undefined in that a specific amount of time has not been recited.

Claim 21 is indefinite because the limitation "different dosage units" could signify a variety of elements. What are the "different dosage units" Applicant is referring to?

* * * * *

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-41 of copending Application No. 10/690,947. Although the conflicting claims are not identical, they are not patentably distinct from each other because co-pending '947 application also claims a (method of making) milnacipran formulation in delayed or extended release form to produce a therapeutic effect over approximately 24 hours, whereby the formulation provides for diminished incidence or reduced intensity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paillard *et al.* (U.S. Patent No. 6,699,506) in view of Perry (U.S. Patent No. 6,066,643) and further in view of Mylari (U.S. Patent No.6,380,200).

The instant invention is drawn to a milnacipran formulation that provides delayed or extended release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects.

Paillard *et al.* ('506) teach a prolonged release oral administration formulation of milnacipran. The formulation comprises a single daily dose of 60 to 140 mg of milnacipran having a multi-particulate form containing a plurality of microgranules each comprising an active microsphere containing a saccharose and/or starch nucleus and containing 150 to 1000 μm of milnacipran and a binding agent, whereby each microgranule is coated with a film, with a base of at least one polymer insoluble in water but permeable to physiological liquids. Paillard *et al.* teach that between 10 and 55% of the milnacipran dose is released in 2 hours, between 40 and 75% of the dose is released in 4 hours, between 70 and 90% of the dose is released in 8 hours and between 80 and 100% of the dose is released in 12 hours (see Abstract); (col. 1, line 4 – col.2, line 9).

Coating agents employed include derivatives of acrylic copolymers, alkyl celluloses, ethyl cellulose and lacquers of natural origin such as shellac gum (col. 6, lines 45-51).

Methacrylic copolymers marketed under the trade name Eudgragit can be used (col. 6, line 52 – col. 7, line 30).

Paillard et al. teach an extended release formulation of milnacipran. Paillard et al. do not teach at least one additional active compound and do not explicitly teach the reduction of side effects. However, it is the position of the Examiner that the milnacipran formulation of Paillard et al. would provide for beneficial therapeutic effects as desired by Applicant. Paillard et al. teach administration of a daily dosage amount of milnacipran of 60 to 140 mg that falls within the dosage range of 25 to 500 mg claimed by Applicant (instant claims 16-17). The reference also recognizes that between 10 and 55% of the milnacipran dose is released in 2 hours, which would entail the range of Applicant's instant claim 4. The reference also teaches coating granules with an overcoating of an insoluble polymer. In any event, Perry is relied upon for the teaching of the reduction of side effects associated with administration of an SSRI and for the teaching of an additional active compound.

Perry ('643) teaches a method for producing a potentiating effect on the therapeutic action of a selective serotonin reuptake inhibitor (SSRI) whereby milnacipran is administered with moxonidine - an antihypertensive agent. The potentiating effect may be an efficacy enhancing effect or an onset enhancing effect or both (see reference column 1, line 3 – col. 2, line 39); (col. 5, line 59 – col. 6, line 15) and Abstract. Perry teaches that the compositions may be formulated to provide quick, sustained or delayed release of the active ingredient after administration to the patient (col. 6, lines 46-59). The reference recognizes and suggests that co-

administration of the SSRI (i.e., milnacipran) in combination with moxonidine provides for the alleviation of side effects.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an additional active agent, such as the antihypertensive agent – moxonidine with a SSRI (i.e., milnacipran) as taught by Perry within the extended release milnacipran pharmaceutical composition of Paillard et al. One of ordinary skill in the art would do so because Perry teaches that co-administration of the SSRI, such as milnacipran with moxonidine can provide for a potentiating effect on the therapeutic action of the SSRI with diminished side effects. The expected result would be an enhanced, highly effective extended release milnacipran formulation for the beneficial treatment of depression.

The teachings of Paillard et al. and Perry are discussed above.

Paillard et al. do not teach a kit comprising milnacipran.

Mylari ('200) teaches methods, pharmaceutical compositions and kits comprising an aldose reductase inhibitor (ARI) and selective serotonin reuptake inhibitor (SSRI) (see Abstract); (col. 2, lines 1-17); (claims 24-27). A preferred SSRI disclosed is milnacipran (col. 2, lines 25-33).

The kit comprises separate pharmaceutical compositions comprising an ARI and SSRI. Typically, the kit comprises directions for the administration of the separate components. Mylari teaches that kits are particularly advantageous when the separate components are administered in different dosage forms (e.g. oral and parenteral), are administered at different dosage intervals or

when titration of the individual components of the combination is desired by the prescribing physician (col. 8, line 45 – col. 9, line 42).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a kit form for containing milnacipran formulations, as taught by Mylari with the milnacipran formulations disclosed by Paillard et al. One of ordinary skill in the art would do so because Mylari explicitly teaches that kits are particularly advantageous when separate components are administered in different dosage forms, are administered at different dosage intervals or when titration of the individual components of the combination is desired. The expected result would be a convenient container that can hold one or more active agents for administration of separate pharmaceutical compositions in kit form.

* * * * *

Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paillard *et al.* (U.S. Patent No. 6,699,506) in view of Michelson et al. (WO 99/59593) and further in view of Mylari (U.S. Patent No.6,380,200).

The instant invention is drawn to a milnacipran formulation that provides delayed or extended release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects.

Paillard *et al.* ('506) teach a prolonged release oral administration formulation of milnacipran. The formulation comprises a single daily dose of 60 to 140 mg of milnacipran having a multi-particulate form containing a plurality of microgranules each comprising an

active microsphere containing a saccharose and/or starch nucleus and containing 150 to 1000 μm of milnacipran and a binding agent, whereby each microgranule is coated with a film, with a base of at least one polymer insoluble in water but permeable to physiological liquids. Paillard *et al.* teach that between 10 and 55% of the milnacipran dose is released in 2 hours, between 40 and 75% of the dose is released in 4 hours, between 70 and 90% of the dose is released in 8 hours and between 80 and 100% of the dose is released in 12 hours (see Abstract); (col. 1, line 4 – col.2, line 9).

Coating agents employed include derivatives of acrylic copolymers, alkyl celluloses, ethyl cellulose and lacquers of natural origin such as shellac gum (col. 6, lines 45-51). Methacrylic copolymers marketed under the trade name Eudgragit can be used (col. 6, line 52 – col. 7, line 30).

Paillard et al. teach an extended release formulation of milnacipran. Paillard et al. do not teach at least one additional active compound and do not explicitly teach the reduction of side effects. However, it is the position of the Examiner that the milnacipran formulation of Paillard et al. would provide for beneficial therapeutic effects as desired by Applicant. Paillard et al. teach administration of a daily dosage amount of milnacipran of 60 to 140 mg that falls within the dosage range of 25 to 500 mg claimed by Applicant (instant claims 16-17). The reference also recognizes that between 10 and 55% of the milnacipran dose is released in 2 hours, which would entail the range of Applicant's instant claim 4. The reference also teaches coating granules with an overcoating of an insoluble polymer. In any event, Michelson et al. are relied upon for the teaching of the reduction of side effects associated with administration of an SSRI and for the teaching of an additional active compound.

Michelson *et al.* ('593) teach a pharmaceutical composition and method comprising a first component – $5HT_3$ receptor antagonist and a second component comprising a selective serotonin reuptake inhibitor (SSRI) (see Abstract and page 2, lines 12-36). Suitable SSRI's disclosed include milnacipran (p. 4, lines 25-31); (p. 11, lines 29-31). Combinations of two or more SSRI's may be used (p. 5, lines 28-35). The compositions of Michelson et al. provide for the reduction of gastrointestinal side effects associated with administration of SSRI's, such as nausea, vomiting and diarrhea (p. 1, lines 27-32); (p. 10, lines 28-30); (claim 8).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an additional active agent, such as the $5HT_3$ receptor antagonist as taught by Michelson et al. within the extended release milnacipran pharmaceutical composition of Paillard et al. One of ordinary skill in the art would do so because Michelson et al. teach co-administration of an SSRI, such as milnacipran with $5HT_3$ receptor antagonist (zatosetron) and teach that their composition can provide for multiple benefits, including reduction of gastrointestinal side effects caused by intake of SSRIs, such as nausea and vomiting. The expected result would be an improved extended release milnacipran formulation for effectively treating depression.

The teachings of Paillard et al. and Michelson et al. are discussed above.

Paillard et al. do not teach a kit comprising milnacipran.

Mylari ('200) teaches methods, pharmaceutical compositions and kits comprising an aldose reductase inhibitor (ARI) and selective serotonin reuptake inhibitor (SSRI) (see Abstract); (col. 2, lines 1-17); (claims 24-27). A preferred SSRI disclosed is milnacipran (col. 2, lines 25-33).

The kit comprises separate pharmaceutical compositions comprising an ARI and SSRI. Typically, the kit comprises directions for the administration of the separate components. Mylari teaches that kits are particularly advantageous when the separate components are administered in different dosage forms (e.g. oral and parenteral), are administered at different dosage intervals or when titration of the individual components of the combination is desired by the prescribing physician (col. 8, line 45 – col. 9, line 42).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a kit form for containing milnacipran formulations, as taught by Mylari with the milnacipran formulations disclosed by Paillard et al. One of ordinary skill in the art would do so because Mylari explicitly teaches that kits are particularly advantageous when separate components are administered in different dosage forms, are administered at different dosage intervals or when titration of the individual components of the combination is desired. The expected result would be a convenient container that can hold one or more active agents for administration of separate pharmaceutical compositions in kit form.

Conclusion

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours. (Wednesdays - Telework).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

HUMERA N SHEIKH
PRIMARY EXAMINER
Art Unit 1615

September 17, 2007

hns